A COMPARATIVE STUDY OF INTRATHECALLY ADMINISTERED FENTANYL AND MIDAZOLAM WITH INJ.BUPIVACAINE FOR PREVENTION OF NAUSEA AND VOMITING DURING CAESAREAN DELIVERY

A STUDY OF 100 CASES

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CHENNAI.

CERTIFICATE

This is to certify that the dissertation entitled " **A COMPARATIVE STUDY OF INTRATHECALLY ADMINISTERED FENTANYL AND MIDAZOLAM WITH INJ.BUPIVACAINE FOR PREVENTION OF NAUSEA AND VOMITING DURING CAESAREAN DELIVERY**" is a bonafide record work done by **DR.V.KRITHIKA**, in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

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DECLARATION

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This is submitted to the Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment of the regulations for the award of MD degree Branch – **X [Anaesthesiology].**

Date :

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Last,but not the least, I gratefully acknowledge the patients who gave their consent and co-operation for the study.

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INTRODUCTION

The most common and distressing symptoms which follow anaesthesia and surgery are pain and emesis. Sometimes nausea and vomiting may be more distressing especially after minor and ambulatory surgeries,delaying the hospital discharge. It may be a major factor in upsetting the intra-operative period and post-operative convalescence.

It is common after spinal anaesthesia for caesarean section with reported incidence as high as 66%. Available large number of agents which prevent emesis indicate the magnitude of the problems and lack of satisfactory results.

Nausea and vomiting has been associated for many years in use of general anaesthesia (i.e.)ether and chloroform. Extensive description of postoperative nausea and vomiting has been given by Sir John Snow in 1948 within 18 months of chloroform introduction.

In pregnancy, there is always an increased frequency of nausea and vomiting due to various factors. When these are added to the effects of sympathetic block in spinal anaesthesia, may increase the frequency of nausea and vomiting in the post-operative period starting from intra-operative period.

One of the major factors in this regard is visceral pain and pain resulting

from traction of peritoneum. The present study is done to compare the effectiveness of adding fentanyl and midazolam with Bupivacaine and saline added with bupivacaine in preventing the incidence of intra-operative and post-operative nausea and vomitingThis study is undertaken with utmost care and the results are discussed.

AIM OF THE STUDY

To compare the efficacy of fentanyl and midazolam co-administered with bupivacaine in reducing the incidence of nausea and vomiting during caesarean section under spinal anaesthesia.

HISTORICAL ASPECTS IN POSTOPERATIVE NAUSEA AND VOMITING

During ether era, reported incidence of post operative nausea and vomiting was as high as 75-80%. Various techniques including olive oil and glucose insulin injection were reported to be effective as reported by Robert Ferguson in 1912. The effect of atropine was appreciated by Brown Sequard as early as 1883.

In the second half of the century the incidence of post operative nausea and vomiting decreased to about 50%due to the use of non opoid, non-ether, regional anaesthetic techniques, refinement of surgical techniques and identification of patient's protective emetogenic factors. There are 3 kinds of vomiting, the first of which is attributed to anaesthetics such as ether, second due to the reflex responses, third due to the medication used intraoperatively. Subsequent investigation unfolded a spectrum of non-anaesthetic factors in the pathogenesis of post operative nausea and vomiting.

Over years numerous drugs have been used in the management of post operative nausea and vomiting. Phenothiazines were synthesized in late 19th century by chemists in dyeing industry. Promethazine was found in 1930 to have good anti-emetic property. However sedative action of it, limited its use. Phenothiazine derivatives have been exclusively used in the treatment of post operative nausea and vomiting.

The recent introduction of the 5HT3 antagonists such as ondansetron and granisetron have reached good heights in the treatment of nausea and vomiting.

There are new antiemetics like neurokinin-1, (substance-P antagonists)in development.

The reason for the magnitude of the problem of PONV persisting inspite of the various drug in use can be assessed by four factors.

1. **Complexity of the problem:** The variables are that it becomes difficult to assess the effects of an intervention as it requires considerable number of patients of well controlled trials.
2. **Inadequate qualification of phenomena:** The phenomenon has been poorly qualified i.e.nausea, vomiting, retching etc.

3. **Inadequate antiemetic regimen:** Unable to identify a good drug which can prevent nausea and vomiting.
4. **Animal Model:** A lack of model to study the physiology and pharmacology of mechanism of PONV. Though monkey and dogs are available they don't suffer from pregnancy induced vomiting and motion sickness and post operative and post anesthetic emesis.

HISTORY

SUB ARACHNOID BLOCK:

The first neuraxial block was performed by James Leonard Corning, who also coined the term "Spinal anesthesia" on October 12, 1865. He injected cocaine 120mg between T11 and T12 spinous process, and obtained loss of sensation due to epidural block rather than a subarachnoid block.

Further advances took place in Keil, Germany where August Bier and his assistant August Hilderbrant used Quinke's method to enter the intrathecal space and injected 5-15mg of cocaine to produce spinal anesthesia. This happened on August 16, 1898.

This was followed by successful and enthusiastic practice of spinal anesthesia by others:

- J.B Selclowitsch of St.Petersburg on May11, 1899
- Theodre Juffier in France on November 9, 1899 and

- Rudolph Mates in New Orleans in November 10, 1899.

Barker advised meticulous sterile technique and introduced hyperbaric solutions.

Serious complications from spinal anesthesia were soon observed. In 1900,F.Gumprecht observed 15 cases of sudden death from lumbar puncture.

LOCAL ANAESTHETICS:

1855 : Friedrich Gaedicke of Germany isolated the first local anaesthetic agent cocaine.

1860 : Albert Neimann purified and named the alkaloid as cocaine.

1884 : Carl Koller an opthalmalogist from Vienna demonstrated the analgesic properties of cocaine on the cornea.William Halstead recognized the ability of injected cocaine to interrupt nerve impulse conduction, leading to the introduction of peripheral nerve block anaesthesia and spinal anaesthesia.

1885 : J.L.Corning produced analgesia by neuraxial injection of cocaine.

1904 : Ernest Foureau Synthesized stovaine.

1905 : Einhorn introduced the first synthetic local anaestheic, procaine.

1943 : Lofgren synthesized the first amide local anaesthetic, lidocaine.

1947 : Torsten Gordh made the first clinical use of lidocaine.

1957 : Ekenston et al of Sweden synthesized bupivacaine.

1963 : L.J.Tulivuo first used bupivacaine, clinically.

OPIOIDS:

1803 : Morphine was isolated from opium by Serturner.

1832 : Codeine was isolated.

1848 : Papavarine was introduced.

1939 : Meperidine was synthesized and it was used for anaesthesia with nitrous oxide.

1942 : Nalorphine a mixed agonist- antagonist was introducecd.

BENZODIAZEPINES:

Benzodiazepines were discovered to be effective sedative and hypnotic drugs.

1955 : Sternbach synthesized chlordiazepoxide.

1959 : Sternbach synthesized diazepam.

1961 : Oxazepam, a metabolite of diazepam was synthesized by Bell.

1971 : Lorazepam was introduced. It was the first clinically used water soluble benzodiazepine.

1977 : Specific receptor for benzodiazepines was identified.

Midazolam was the first benzodiazepine that was produced primarily for use in anaesthesia.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid local anaesthetics effect their sensory block at the spinal cord, which is continuous cephalad with the brain stem via foramen magnum and terminates distally in the conus medullaris. The distal termination, because of differential growth rates between bony vertebral canal and central nervous system, varies from L_3 in the infant to L_1 in the adult.

Surrounding the spinal cord in the bony vertebal column are three membranes (from within to periphery) : the piamater, arachnoid mater and duramater. The piamater is a highly vascularised membrane that closely invests the spinal cord. The arachnoid mater is a delicate non vascular membrane closely attatched to the outermost layer, the duramater. Between these two innermost layers is the space called as subarachnoid space. In this space are the CSF, spinal nerves, a trabecular network between two membranes, blood vessels that supply the spinal cord and the lateral extensions of the piamater and the dentate ligaments, which provide lateral support from the cord to the duramater.

Although the spinal cord ends at L_1, the subarachoid space continues to S_2. The third and the outermost layer in the spinal cord is the longitudinally organized fibroelastic membrane, the duramater. This layer is the direct extension of the cranial dura and extends as spinal dura from the foramen magnum to S_2 where the filum terminale blends with the coccyx.

THE ANATOMY OF AREAS INVOVED IN CONTROL OF VOMITING

There are two areas which control or take part in the modulation of vomiting process.

i) The vomiting centre

ii) The chemoreceptor trigger zone.

The vomiting centre

The vomiting centre is located in the reticular formation of the medulla oblongata. It takes part in the initiation of vomiting when they are stimulated by certain circulating chemical agents.

The chemoreceptor trigger zone

This centre is in or near the area postrema as a 'V' shaped tissue in the lateral wall of the 4^{th} ventricle near the apex. It's a circumventricular organ. This area is stimulated by radiation sickness, uremia, morphine and other emetic agents.

PHYSIOLOGY OF VOMITING

DEFINITIONS

1.Nausea

It is an unpleasant sensation referred to as a desire to vomit, not associated with expulsive muscular movement.

2.Retching

When no stomach contents are expelled even with expulsive muscular efforts.

3.Vomiting

It is the forceful expulsion of even small amounts of upper gastrointestinal contents through mouth.

There are three major components of vomiting reflex, emetic detectors, integrative mechanism and motor output.

The main sensors of somatic stimuli are located in the gut and chemoreceptor trigger zone.

The emetic stimuli are detected from gut by 2 types of vagal afferent fibres.

a) **Mechanoreceptor :** Located in muscular wall of the gut and are activated by

contraction and distension of the gut, on physical damage and manipulation during surgery of proximal gut may induce vomiting in over eating.

b) **Chemoreceptors:** They are situated in the mucosa of upper gut and are sensitive to noxious stimuli.

The CTZ (Chemoreceptor Trigger Zone) lies in the area postrema, which is able to detect the circulatory toxins in the CSF and activates the vomiting centre in the medulla. Afferent impulses from other areas like vestibular labyrinth ,input from limbic system and visual cortex can stimulate it.The vomiting reflex is divided into two phases.

i) The pre-ejection phase

This is characterized by a sensation of nausea associated with cold,

sweating, pupil dilatation, salivation and tachycardia mediated by sympathetic and para sympathetic nerves.

ii) The ejection phase

This consists of retching and vomiting with expulsion of gastric contents.

Causes of vomiting

- Pharyngeal Stimulation
- Gastrointestinal distension

- Abdominal surgery
- Anaesthetic agents
- Pain
- Opioid medication
- Hypoxia – hypotension
- Hypertension
- Vestibular disturbances
- Psychological factors
- Pregnancy / Hormones

Factors influencing post operative emesis

1. Patient factors
2. Pre operative factors
3. Intra operative factors
    a. Anaesthesia factors
    b. Anaesthetic techniques
    c. Surgical factors
4. Post operative factors

Vestibular cardiac afferents can also stimulate the vomiting centre as in myocardial infarction.

The vomiting centre in medulla is also in close proximity to other visceral centres like respiratory and vasomotor centres. Four types of receptors are involved in vomiting.

- Cholinergic receptors (M)
- Dopaminergic receptors(D2)
- Histamine receptors(H1)
- Serotonergic receptors(5HT3)

Integrative mechanism

It's a co-ordination between many physiological systems and autonomic and somatic components of nervous system which occurs in brain stem.

The motor component of vomiting reflex is mediated by both autonomic and somatic sense, and is coordinated by the vomiting system in the brain stem. The vagal neurons that supply the gut and the heart originate in the dorsal motor vagal nucleus and nucleus ambigus. The dorsal and ventral respiratory group which regulate the phrenic nerve output from the cervical plexus, are parasympathetic neurons. The output of these nuclei are coordinated to produce the physiologic pattern associated with vomiting.

The vomiting reflex

The act of vomiting is a complex, almost convulsive reflex manoeuver involving both visceral and striated muscle. Vomiting begins with deep inspiration, elevation of the soft palate to occlude the naso pharynx and glottic closure. Then the proximal area of the stomach relaxes and a giant contraction of the small intestine forces the previously ingested contents to the stomach diluting and buffering the gastric acid. Finally the contraction of the oesophageal muscles pull the stomach into the thorax forming an oesophageal funnel and food is forced out of the stomach by contraction of the abdominal muscles against the lowered diaphram. If glottis is closed only retching occurs, if the pharynx is relaxed the content is exited through the mouth.

Several autonomic signs precede vomiting. The warning signs include excessive salivation, dilated pupils, tachypnoea, swallowing, pallor sweating and tachycardia. If nausea proceeds to retching bradycardia may replace tachycardia.

PEPTIDES IMPLICATED IN CAUSING NAUSEA AND VOMITING

Nor-epinephrine

ACTH

Vasopressin

Human chorionic gonadotropin

Angiotensin-II

Leu-Enkephalin

Mer. Enkephain

Cholecystokinin

Insulin

Gastrin

Oxytocin

Bombesin

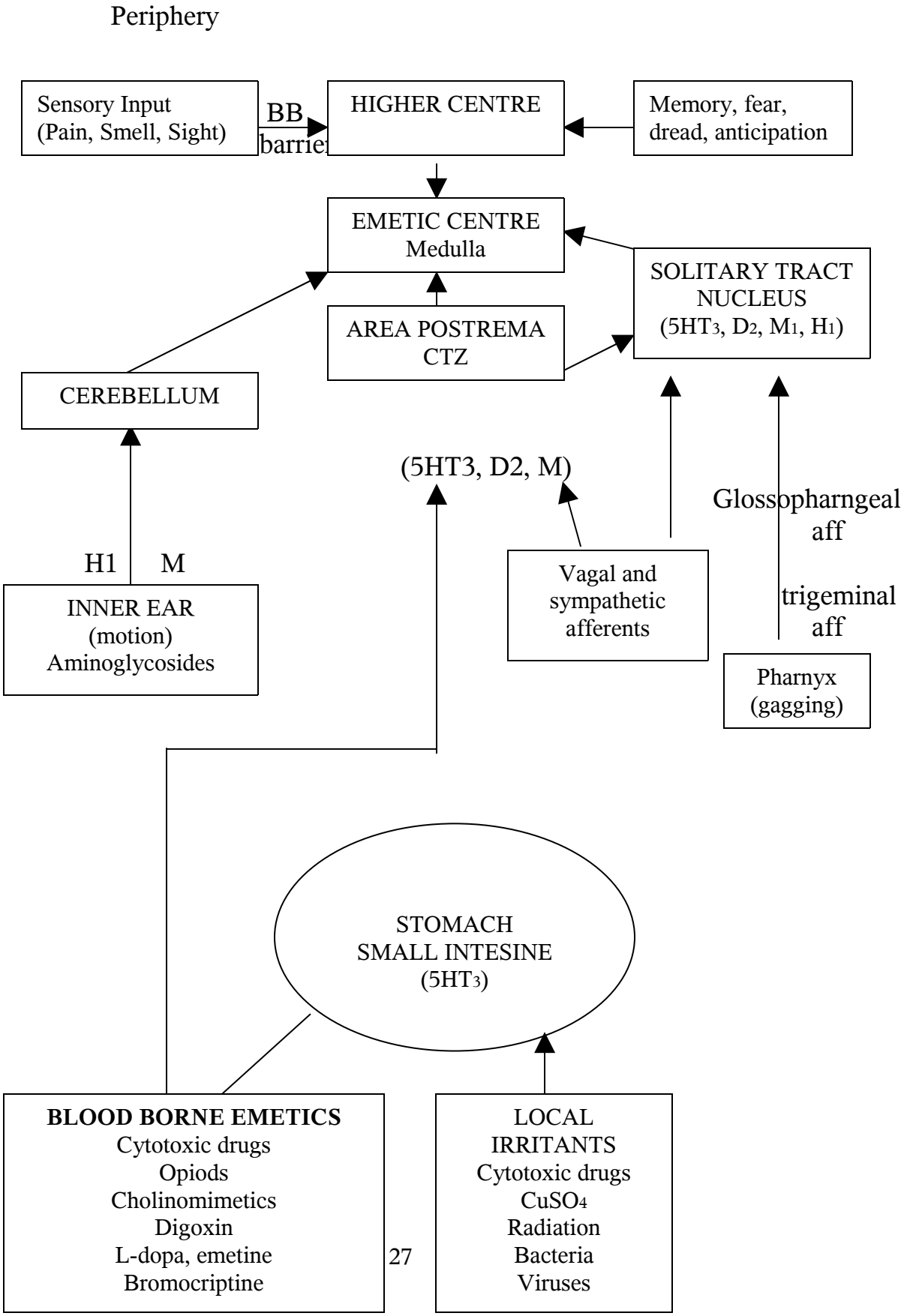
Thyrotropin releasing hormone

Peptide 77

Neurotensin

Vasoactive intestinal peptide

PHARMACOLOGIST VIEW OF EMETIC STIMULI



FACTORS WHICH LEAD TO INCREASED RISK OF PONV IN PREGNANT PATIENTS DURING CAESAREAN SECTION

PATIENT FACTORS

1. There is always increased anxiety, stress and pain when the female is coming for caesarean section which itself increases the risk of PONV,.
2. The retardation of gastro-intestinal motility
3. Increased compression of the stomach due to the gravid uterus may cause a problem.
4. Decreased lower oesophageal sphincter tone due to the hormone progesterone has an increased risk of vomiting.
5. The presence of female hormone oestrogen, progesterone, human chorionic gonadotropin in increased levels, add to the risk of nausea and vomiting.
6. Anatomical changes in oesophago-gastric junction
7. The addition of any opioids or other analgesics in the labour room or ward may in turn increase the risk of nausea and vomiting.

INTRAOPERATIVE FACTORS

1. Intraoperative hypotension: Intra operative hypotension has a greater influence in the occurence of nausea. When there is a greater degree of hypotension, there is increased risk of nausea &vomiting.
2. Intraoperative O_2 supplementation: It has been found out that O_2 supplementation during caesarean section have reduced the incidence of PONV.
3. Intraoperative medications: Intra operative medications given systemically such as prostglandins, methergine have increased the incidence of postoperative nausea and vomiting.
4. Surgical factors:
    i. compression of uterus from outside the abdominal cavity to deliver the baby , has an increased role to play in the riskof nausea and vomiting.
    ii. The manual delivery of placenta by compression of uterus and pulling the umbilical cord, is one of the important periods, where the patient complains of nausea.

iii. The exteriorization of the uterus to secure the bleeding points and compressing the uterus to prevent post partum hemorrhage, pull the peritoneal attachments and have increased vagal discharge, which is critical to the occurence of nausea and vomiting.

POST OPERATIVE FACTORS

i) Anxiety plays an important role in the post operative period.

ii) The quick descent of the local anaesthetic,and thereby patient experiencing pain, may increase the risk of post-operative nausea and vomiting.

iii) Early ambulation may have an important role to play in PONV.

iv) Early oral feeds may also cause increased incidence of PONV.

ADJUVANTS TO LOCAL ANAESTHETICS IN SPINAL ANAESTHESIA

Local anesthetic agents have been widely used in spinal anaesthesia. One of the main disadvantages is the limited duration of block achieved with local anaesthetics. To overcome this, various adjuants have been tried and used successfully. This addition of adjuant has further expanded the advantage of regional anaesthesia over general anaesthesia.

ADJUANTS:

These may be opioids like morphine,fentanyl, sufentanil or buprenorphine. It may be benzodiazepines, alpha 2 agonist clonidine, acetylcholine esterase inhibitors like neostigmine,NMDA receptor antagonist ketamine or nonsteroidal anti inflammatory agents.

These adjuants usually confer the advantage of

- Rapid onset time
- Differential blockade
- Inhibition of tourniquet pain
- Improved and prolonged duration of post operative analgesia
- Inhibition of visceral pain/pain associated with peritoneal

traction.

Also these adjuants decrease the amount of local anaesthetic required to produce the same effect thereby reducing the risk of local anaesthetic toxicity, hypotension and profound motor blockade.

OPIOIDS

The term opioids refer to all compounds related to opium, derived from juice of opium poppy, papaver sommniferum. Opiates are the term used for drugs derived from opium. Morphine is the prototype opioid. Opioid compounds can be classified as naturally occuring,semisynthetic and synthetic opioids. With the development of synthetic drugs with morphine like effects, the term opioid is now used to refer to all exogenous substances, natural and synthetic that binds to opioid receptors and produces some agonisitic effects.

CLASSIFICATION:

Naturally occurring opioids are divided into two chemical classes

1. Phenanthrene-eg. Morphine and codeine
2. Benzylisoquinolines-eg. Papavarine

Semisynthefic opioids result from relatively simple modification of morphine molecule.eg.diacetylmorphine.

Synthetic opioids contain phenanthrene nucleus. They are classified into

four subdivisions.

1. Morphinan derivative-eg.levorphanol
2. Methadone derivative-eg.methadone

3. Benzomorphan derivatives-eg.pentazocine
4. Phenylpiperidine derivatives-eg.meperidine, fentanyl, sufentanil,alfentanil

OPIOID RECEPTORS:

The presence of opioid binding sites in the nervous system was reported in the year 1973. Immuno histochemical studies have demonstrated opioid receptors in various areas of the central nervous system. These include the amygdala, the mesencephalic reticular formation, the periaqueductal gray matter and the rostral ventral medulla.

Based on pharmacological experiments three types of opioid receptors were published.

(i) mu or μ for morphine type

(ii) Kappa or K for Ketocyclazocine type

(iii) Sigma or σ for SKF 10047 type

In addition two other receptors have been identified in vas deferens of mouse namely the delta ($^{\delta}$) and epsilon(Σ) receptors. All the receptors bind to a super family guanidine protein coupled receptors.

The μ or morphine preferring receptors are principally responsible for supra spinal and spinal analgesia. Various subtypes have been proposed based on post translational modification of μ receptor. μ_1 receptor is speculated to produce analgesia. While μ2 receptor is responsible for hypotension, bradycardia and respiratory depression. Delta receptors serve to modulate the activity of μ receptor. Kappa receptors are those to which most of the opioid agoinst-antagonist bind. Respiratory depression is less common with Kappa receptor activation than μ. Dysphoria and diuresis may occur. High intensity painful stimulations are resistant to the analgesic effect of Kappa receptor activation.

CHARACTERISTICS OF OPIOID RECEPTORS

		Mu (µ1)	Delta (δ)	Kappa(K)
1	Endogenous Ligand	β-endorphin	Leu-enkephalin Met-enkephalin	Dynorphin
2	Agonist	Morphine Fentany1	DPDPE Deltorphin	Buprenorphine Pentazocine
3	Antagonist	Naloxone Naltrexone	Naloxone Naltrindole	Naloxone BNI
4	Coupled G Protein	Gi/o	Gi/o	Gi/o
5	Adenylate cyclase	Inhibition	Inhibition	Inhibition
6	Effect	Analgesia Supraspinal and spinal (µ1) Euphoria(µ1) Respiratory Depression(µ2) Bradycardia (µ2) Constipation(µ2)	Analgesia Respiratory Depression Constipation (minimal)	Analgesia (Spinal) Dysphoria Sedation Miosis Diuresis

PHARMACOLOGICAL ACTIONS OF OPIOIDS

		Receptor	Action	
			Agonists Antagonists	
1	Suprapinal Spinal	μ,σ,k μ,σ,k	Analgesic Analgesic effect	No effect No
2	Respiratory Function	μ	Decrease effect	No
3	Gastro intestinal Tract	μ, k	Decrease	No effect
4	Psychotomimesis	k	Increase effect	No
5	Feeding	μ,σ,k	 Decrease	Increase
6	Sedation	μ, k	Increase effect	No
7	Diuresis	k	Increase	
8	Hormone Secretion (a) Prolactin (b) Growth hormone	μ μ and σ	Increase Decrease release Increase Decrease release	release release

MECHANISM OF ANALGESIC ACTION:

Opioids act as agonists at stereospecific opioid receptors at presynaptic and post synaptic sites in the central nervous system and also outside central nervous system in peripheral tissues.

MECHANISM OF ACTION IN CENTRAL NERVOUS SYSTEM:

The analgesic effect of opioids result from their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn. It has a descending inhibitory analgesic action by activation of pain control circuits that descend from the midbrain via the rostral ventromedial medulla (RVM) to the spinal cord dorsal horn. In addition,local spinal mechanisms also take part in the analgesic action of opioids.

Existence of the opioids in the ionized state is necessary for strong binding at the anionic opioid receptor site. Stereochemically,levorotatory forms are found to be most active. The affinity of most opioid agonists for receptors correlated with their analgesic property.

The principal effect of opioid receptor activation is a decrease in neuro transmission. This decrease in neuro transmission is largely due to presynaptic inhibition of neurotransmitter release, although post synaptic evoked activity may also occur.

The neurotransmitters whose releases are also inhibited include acetylcholine, dopamine, norepinephine and substance P.

The intracellular biochemical events activated by binding of opioid agoinst to opioid receptor are:

(i) Increased potassium conductance-leading to hyperpolarization

(ii) Calcium channel inactivation

Both of which produce an immediate decrease in neurotransmitter release.

Opioid receptors mediated inhibition of adenylate cyclase,causing a decrease in cellular cAMP has a delayed effect, via a reduction in cAMP responsive neuropeptide agent and a reduction in neuropeptide mRNA concentrations.

MECHANISM OF ACTION IN PERIPHERAL TISSUES:

Opioids are effective in inflammatory hyperalgesic conditions. The

opioids bind to receptors in the primary afferent neurons and mimic the action of endogenous ligands, resulting in the activation of pain modulating (antinociceptive) systems.

EFFECT OF OPIOIDS ON VARIOUS SYSTEMS OF THE BODY:

These can be classified into therapeutic drug effects and non-therapeutic drug effects.

THERAPEUTIC DRUG EFFECTS:

OPIOIDS AS ANAESTHETICS:

The capacity of opioids to produce anesthesia is debated. General anaesthesia can be considered in terms of its component parts: amnesia, analgesia, unconsciousness, immobility,muscle relaxation and control of autonomic and endocrine response to surgery.

Of these, opioids produce effects of analgesia, unconsciousness and control of autonomic and endocrine response to surgery. Butorphanol has been reported to produce anterograde amnesic effect.

Shivering: Post anaesthetic shivering,that is unrelated to hypothermia can be effectively abolished by certain opioids like meperidine, butorphanol and tramadol.

CENTRAL NERVOUS SYSTEM:

Opioids generally produce modest decrease in cerebral metabolic rate (CMR). They cause decrease in cerebral blood flow when co administered

with nitrous oxide and a cerebral vasodilating anaesthetic. Opioids affect intracranial pressure minimally, but may cause increase in intracranial pressure when compliance is compromised.

NON THERAPEUTIC DRUG EFFECTS:

While opioids have proved to be relatively safe drugs, management of side effects is critical to successful application in clinical practice.

RESPIRATORY EFFECTS:

Opioids decrease resting minute ventilation and tidal volume. Respiratory rate may be decreased or normal, whereas μ agonists produce a dose related depression of breathing. Ventilatory response to hypoxia and hypercarbia are blunted. Sufficient doses may produce apnoea, but the apnoeic conscious patient may breathe on command.

CARDIOVASCULAR EFFECTS:

The action of opioids on cardiovascular system is mostly due to histamine release.

Morphine or meperidine which cause release of histamine provide hypotension and tachycardia.

Opioids also depress contractility of isolated heart muscle, but at doses greatly in excess of those used clinically. An exception to this is meperidine which produce myocardial depression at clinically relevant concentrations. Morphine and fentany1 analogs decrease heart rate due to vagomimetic action. On the other hand, meperidine due to its anticholinergic properties increase heart rate.

RIGIDITY:

Opioid induced muscle rigidity occurs usually during induction of anaesthesia, especially with larger doses. This rigidity is central in origin, being mediated by μ receptors in brainstem medulla.

NEUROEXCITATORY EFFECTS:

Opioids are also associated with tonic-clonic movements or myoclonus.

GASTRO INTESTINAL EFFECTS:

These effects manifest by a combination of central and peripheral actions. The effects observed are decrease in intestinal motility and increase in the tone of sphincter of Oddi. Nausea and vomiting is a commonly observed effect of opioids due to its stimulation of receptors at chemoreceptor trigger zone.

PRURITUS:

It is a common opioid-induced side effect, especially with neuraxial opioids.

INTRATHECAL OPIOIDS

In the context of "Augmentation strategies" for spinal anaesthesia, the discovery of opioid receptors and the development of technique of intrathecal opioid administration is one of the most significant advances in pain management in the last three decades. Plethora of studies have shown that spinal opioids can provide profound post operative analgesia with fewer neurological and systemic side effects than with systemic opioids. This is because neuraxial opioids, in contrast to local anaesthetics, do not cause sympathetic block, skeletal muscle weakness or lack of proprioception.

BRIEF HISTORY:

In 1900, Matas discovered that the adverse effects of intrathecally administered cocaine could be mitigated with the addition of morphine. He used 1.5mg morphine intrathecally to reduce the central nervous system effects of cocaine.

In 1901, a Japanese anesthesiologist Otojiro Kitagawa, used 10mg of morphine with local anaesthetic eucaine intrathecally for cancer pain relief.

With the discovery of opioid receptors in the spinal cord, intrathecal opioid administration quickly spread to perioperative care in a wide array of surgical procedures.

PHARMACODYNAMICS:

The exact mechanism of local anaesthetic-opioid interaction remains unknown despite detailed characterization of opioid receptor system at the cellular and molecular level.

When administered alone,spinal opioids selectively modulate C and A fibres with minimal impact on dorsal root axons. Somatosensory evoked potentials remain intact with respect to nerve conduction block. None of the opioids exhibit local anaesthetic property except possibly meperidine.

Local anaesthetics potentiate the antinociceptive effect of morphine, without an enhancement in motor block. Transient change in temperature perception has been observed with spinal meperidine, fentanyl and sufentanil.

The dorsal root entry zone is speculated to be active site for conduction block

for spinal opioids. The hormonal milieu (pregnancy) also contributes to drug effectiveness. Spinal progesterone has been found to potentiate the analgesic effects of spinal sufentanil in rats.

PHARMACO KINETICS:

It is beleived that hydrophilic opioids remain unbound in the CSF for a long time and hence to move rostrally in the CSF, thereby resulting in delayed respiratory depression.(eg) morphine.

In contrast lipophilic opioids do not move rostrally in CSF, but move more rapidly than hydrophilic opioids from CSF to spinal cord. But recently, studies have shown that even lipophilic opioids do not remain localized near their site of injection and they may rapidly move from lumbar intrathecal injection sites to cervical and brain stem levels via CSF.

ONSET OF ACTION:

Lipophilic opioids spread more rapidly from the CSF into the spinal cord. Hence they have faster onset of action (eg.fentanyl) than hydrophilic opioids. The delayed onset of action of morphine, a hydrophilic opioid may in fact limit its utility as an intra operative adjuant.

ANALGESIC MECHANISMS:

The effects of intrathecally administered opioids are determined by the pharmacodynamics and pharmacokinetics of each individual drug. The dorsal horn of the spinal cord is richly populated with opioid receptors. Majority of these are localized within substantia gelatinosa. Upon receptor activation, a G protein mediated effect result in inhibition of adenyl cyclase and inward flux of potassium. This flux results in membrane hyperpolarization and decrease in neural excitability (anti nociceptive effect). Opioids may act at synapses in spinal cord either presynaptically or postsynaptically.

μ receptor activation results in the presynaptic inhibition of substance

P release, a compound that would otherwise result in the activation of an integrated pain signal.

All clinically useful intrathecal opioids are strong μ receptor agonists within the dorsal horn. Their supra spinal and spinal effects act synergistically to blunt somatic as well as visceral pain. But analgesic effect is more specific for visceral pain. Analgesia of neuraxial opioids is also dose related.

DURATION OF ACTION:

The duration of analgesic action will depend upon the efficacy,lipophilicity, receptor affinity and the dose of the drug administered. Less lipid soluble drugs (eg morphine) will remain in the CSF for a longer time and hence will produce longer duration of analgesia than a highly lipophilic opioid like fentanyl.

High lipophilicity favours more rapid removal of the drugs from the receptor site into the blood stem,which limits the duration of action, only exception to this being buprenorphine.

POTENCY:

H.J.MCQuay et al in 1989 published that the intrathecal potency is defined as the amount of drug required to produce a particular degree of receptor occupancy. It is inversely related to their lipid solubility and related directly to the affinity of the drug for the receptor. The inverse correlation between intrathecal potency and lipophilicity may be due to the nonspecific binding of highly lipophilic agents to the lipid rich fibres capping the dorsal horn, limiting their access to the receptors. Highly soluble opioid, pethidine, is least potent and has to be used in systemic does for intrathecal administration.

SIDE EFFECTS:

Opioids injected into the lumbar CSF may spread passively cephalad by diffusion and concentration gradient effect,aided by arterial pulsation and respiratory movements over a time course of 6-8 hours. They may reach the vicinity of the cisterna magnum and brain tissue of fourth ventricle. This explains the occurrence of nausea, vomiting and respiratory depression after intrathecal administration.

Incidence of side effects is dose related and larger doses are clearly

associated with higher incidence of side effects.

NAUSEA AND VOMITING:

Opioids commonly produce nausea and vomiting. The vomiting center in medulla receives inputs from many centers including the chemoreceptor trigger zone, which contain opioid receptors among others that promote vomiting. But it has been observed by Dahlgren et al that spinal opioids administred along with local anaesthetics in spinal anaesthesia for cesarean sections decreased the requirement of intraoperative antiemetic medication.

Cooper et al reported a significant reduction in intraoperative nausea with the addition of spinal fentanyl to a spinal anaesthetic for cesaerean delivery. The effects are due to the dense sensory blockade achieved by the addition of opioids to local anaesthetics in spinal anaesthesia.

PRURITUS:

It is a peculiar and the most common side effect with neuraxial opioids. It is not confined to the segmental area of analgesia, but may be generalized or localized to the face, neck or upper thorax. Pruritis is usually very mild, servere pruritis occurring in about 1% patients Pruritis is more likely to occur in obstetric patients, perhaps due to interaction of estrogen with opioid receptors.

Though opioids may release histamine from mast cells, this is not the mechanism for pruritis. Pruritis may be due to a generalized modulation of cutaneous sensation or in the case of neuraxial opioids, due to cephalad migration of the opioid in the CSF and subsequent interaction with opioid receptors in the trigeminal nucleus. Pruritus may or may not be dose related.

URINARY RETENTION:

This is usually encountered with hydrophilic spinal opioids. Urinary retention is most likely due to the interaction of opioids with opioid receptors in sacral spinal cord. This promotes inhibition of sacral

parasympathetic nervous systems outflow causing detrusor muscle relaxation and an increase in maximal bladder capacity. There is also an increase in vesical sphincter tone. All these factors result in urinary retention. This effect is usually not dose related.

RESPIRATORY DEPRESSION:

This is a major problem, limiting the use of spinal opioids. Respiratory depression may occur early or late. Early respiratory depression is usually mild, occurs due to vascular uptake of drugs and occurs within one hour with morphine and within minutes with lipophilic opioids.

Late respiratory depression is more problematic and occurs 4-18 hours following intrathecal administration. This is due to the cephalad spread of drug in the CSF. Highly lipophilic opioids dissolve readily in neural tissue (segmental localization), thus limiting the drug available for cephalad spread. Hence, lipophilic opioids are considered safe with regard to late onset respiratory depression.

Factors which predispose to development of respiratory depression

after intrathecal opioids are advanced age, high risk patients, larger dose of opioids, use of hydrophilic opioids, intrathecal administration as compared with epidural , concominant use of parenteral opioids or sedatives or both, opioid sensitive patients and thoracic epidural administration.

Obstetric patients are at lesser risk for ventilatory depression, perhaps because of the increased stimulation of ventilation by progesterone.

SEDATION:

This effect is dose related. Whenever sedation occurs, depression of ventilation should also be considered.

CENTRAL NERVOUS SYSTEM EXCITATION:

Tonic skeletal muscle rigidity resembling seizure activity is a well known side effect of intravenous opioids, but is rarely observed with neuraxial opioids. Myoclonic activity has been observed after neuraxial opioids. A possible explanation for this effect is the cephalad migration of the opioid in CSF and subsequent interaction with non opioid receptors in the brain stem or basal ganglia. In this regard, opioids may block, glycine and gamma amino butric acid mediated inhibition.

ANTAGONISM:

Systemically administered naloxone can antagonize all the side effects of spinal opioids including repiratory depression. Repeated doses may be required to maintain adequate ventilation. Prophylactic administration of naloxone has also

been recommended by some to prevent pruritus, nausea, vomiting and other side effects. Analgesic effect of intra-thecal opioid is usually not affected by naloxone.

MERITS AND DEMERITS OF SPINAL OPIOIDS:

MERITS:

- Greater success rate of spinal anaesthesia
- Faster onset of surgical block than local anaesthetic alone
- Improved intra operative analgesia (enhanced sensory block without increased

  motor block)
- Reduction in the dose of local anaesthetics with faster recovery from spinal

  anaesthesia
- Post operative analgesia beyond duration of local anaesthetic block
- Less nausea and vomiting

DEMERITS:

- Frequent pruritus
- Sedation (less with lipophilic opioids)

- Rare respiratory depression (especially late onset)
- Rare urinary retention (more with morphine)
- Nausea, vomiting, somnolemce and early respiratory depression due to vascular uptake of opioids. These are dose related.

PHAMACOLOGY OF FENTANYL

Fentanyl is a phenyl piperidine derivative, synthetic opioid agonist that is structurally related to meperidine. As an analgesic fentanyl is 75 to 125 times more potent that morphine.

PHARMACODYNAMICS:

A single dose of fentanyl administered intravenously has a more rapid onset and shorter duration of action than morphine. The effect site equilibrium time is 6.4 minutes. Rapid onset is due to its high lipophilicity and shorter duration of action is due to its rapid redistribution to inactive sites such as fat and skeletal muscles. It is estimated that 75% of initial fentanyl dose is undergoing first-pass pulmonary uptake. When fentanyl is administered as continuous infusion, progressive saturation of these inactive tissue sites occur. As a result, the plasma concentration of fentanyl does not decrease rapidly. So the duration of analgesia, as well as depression of ventilation, may be prolonged.

PHARAMACOKINETICS:

Fentanyl is extensively metabolized by N-demethylation, producing nor- fentanyl, which is structurally similar to normeperidine. Nor fentanyl is excreted by the kidneys and can be detected in the urine for 72 hours after intravenous dose of fentanyl. Even though fentanyl has a short duration of

action, its elimination half life is longer than that for morphine. This is infact due to a larger volume of distribution of fentanyl. The larger volume of distribution is due to its greater lipid solubility and then more rapid passage of drug into tissues compared with less lipophilic morphine. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which account for its persistent effect.

CONTEXT SENSITIVE HALF TIME:

As the duration of continuous infusion of fentanyl increases beyond about 2 hours, the context sensitive half-time of this opioid becomes greater than sufentanil. This reflects the saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces the fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is stopped.

DURING CARDIO PULMONARY BYPASS:

All opioids show a decrease in plasma concentration with the initiation of cardio pulmonary bypass. The degree of this decrease is greater with fentanyl because a significant proportion of the drug adheres to the surface of the cardiopulmonary bypass circuit. Sufentanil and alfentanil may provide a stable plasma concentration during cardio pulmonary bypass. Elimination of fentanyl and alfentanil are prolonged by cardio pulmonary bypass.

CLINICAL USES:

Low dose of fentanyl,1-2mcg/kg, is injected to provide analgesia.Moderate dose of fentanyl, 2-20mcg/kg, is administered as an adjuvant to inhaled anaesthetics to blunt the circulatory responses to (a) direct laryngoscopic intubation (b) sudden change in the level of surgical stimulation. Timing of fentanyl administration to blunt these responses should consider the effect-site equilibration time.

Larger doses of fentanyl, 50 -150mcg/kg have been used alone to produce surgical anaesthesia. The advantage of larger and sole fentanyl

administration are (a) lack of myocardial depressant effect, (b) absence of histamine release, (c) suppression of the stress responses to surgery. Disadvantage include (a) post operative depression of ventilation and (b) possible patient awareness.

Fentanyl may be administered as a oral transmucosal preparation in a delivery device designed to deliver 5-20mcg/kg of fentanyl. In children aged 2 to 8 years, the preoperative administration of transmucosal fentanyl 15-20mcg/kg 45 minutes before the induction of anaesthesia, reliably induces preoperative sedation and facilitates induction of inhalation anaesthesia. But there is more chance of post operative nausea and vomiting in these patients.

Transdermal fentanyl preparation delivering 75 to 100 mcg/hour result in peak plasma fentanyl concentration for about 18 hours that tend to remain stable during the

presence of the patch, followed by decelerating plasma concentration for several hours after removal of the delivery system, reflecting continued absorption from the cutaneous depot.

SIDE EFFECTS:

RESPIRATORY EFFECTS:

Persistent or recurrent depression of ventilation is a potential post operative problem. There are two theories for secondary peaks in plasma concentration of fentanyl.

One is due to sequestration of fentanyl in acidic gastric fluid. This sequestered fentanyl could then be absorbed from the more alkaline small intestine back into the circulation to increase the plasma concentration of opioid and cause depression of ventilation to recur. Second is due to washout of opioid from the lungs as ventilation perfusion relationships are reestablished in the postoperative period.

CARDIOVASCULAR EFFECTS:

Carotid baroreceptor reflex control of heart rate is markedly depressed by fentanyl. Bradycardia is more prominent with fentanyl and may lead to occasional decreases in blood pressure and cardiac output.

CENTRAL NERVOUS SYSTEM EFFECT:

Seizure activity has been described to follow rapid intravenous administration of fentanyl, sufentanil and alfentanil. In the absence of EEG, it is difficult to distinguish opioid-induced skeletal muscle rigidity or myoclonus from seizure acitivity. Opioids may produce a clinical picture of seizure activity in the absence of EEG changes.

Administration of fentanyl and sufentanil to head injury patients has been associated with modest increase in intracranial pressure despite maintenance of an unchanged PaCO2. These increases in intracranial pressure are typically accompanied by decrease in mean arterial pressure and cerebral perfusion pressure.

DRUG INTERACTIONS:

Analgesic concentrations of fentanyl greatly potentiate the effects of midazolam and decreases the dose requirements of propofol. The opioid-benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation.

PHARMACOLOGY OF MIDAZOLAM

Midazolam is a water soluble imidobenzodiazepine. Benzodiazepines were introduced in early 1960s. Diazepam, the most popular drug of this group for the past 2 decades, is water insoluble, has a prolonged effect and is painful during injection. The unique chemical structure of midazolam confers a number of physiochemical properties that distinguish it from other benzodiazepines. This drug was synthesized in 1976 by Tryer and walser.

CHEMISTRY:

Benzodiazepines are so called because they consist of a benzene ring fused with a seven member diazepine ring. Various modification in the structure of the ring systems have yielded compounds with similar activities.

Midazolam with molecular weight of 362, has a fused imidazole that is different from classic benzodiazepines. The imidazole ring accounts for the basicity, stability of an aqueous solution and rapid metabolism. The ring exhibits a **$_{P}$H dependent ring opening** phenomenon. The ring opens at pH

less than 4 making the drug soluble in aqueous solution. Once midazolam enters the body, the pH changes to 7.5 and drug assumes closed ring structure and becomes highly lipid soluble. Midazolam is the most lipid soluble benzodiazepine.

PHARMACOKINETICS:

Midazolam is rapidly absored from gastro intestinal tract, but only 50% of the orally given drug enter the circulation, as substantial portion is metabolized during the first hepatic flow. Thus the oral dose is twice as high as intravenous dose.

Peak plasma concentrations are seen within an hour of ingestion. When given intramuscularly, the absorption is more predictable than diazepam. Being highly fat soluble it crosses blood brain barrier more easily than diazepam, to gain access to the receptors. It has a more rapid onset of action. After intravenous administration of midazolam to healthy adults, the disappearance of midazolam from the plasma proceeds in two distinct phases. The initial phase of rapid disappearance is due principally to distribution of the drug while the final and slower phases of disappearance is

attributable mainly to biotransformation. The volume of distribution averages between 1 and 2.5 1/kg. Midazolam is tightly bound to plasma protein. After distribution equilibrium is reached.Its elimination half-life varies from 1 to 4 hours. Midazolam is metabolized mainly by hepatic microsomal oxidative mechanism, by a process of hydroxylation. The fused imidazole ring is oxidized very rapidly to both 1 and 4 hydroxy midazolam. Both these products are conjugated to glucuronides and are excreted in the urine. The metabolites have less than 1% activity of the parent drug.

FACTORS AFFECTING PHARMACOKINETICS:

1. Old age-Elimination half-life is increased and clearance is delayed.
2. Obesity- The volume of distribution is increased. This increases the elimination half-life, but there is no change in the total metabolic clearance.
3. Renal insufficiency-As less than 1% of midazolam is cleared through the kidney, there is minimal alteration of its clearance in patients with renal insufficiency. The free fraction of midazolam in the plasma is increased due to decreased plasma binding.
4. Pregnancy – Midazolam crosses the placental barrier, but the

placental transmission as judged by foetal – maternal plasma ratio in animals.It is less for midazolam than for diazenpam.

5. Gender – males are more susceptible to midazolam than female patients.

MECHANISM AND SITE OF ACTION:

An important inhibitory neurotransmitter in the brain is gamma amino butric acid (GABA), while glycine is the major inhibitory neurotransmitter in the spinal cord and brainstem. The benzodiazepines augment GABA thus producing sedation and anticonvulsant activity, while anxiolysis and muscle relaxation appear to be due to glycine mimetic effects in the spinal cord and brainstem.

Among the benzodiazepines midazolam has greatest affinity for the receptors, but dissociate faster from the receptor, thus accounting for the rapid onset and shorter duration of action. Given intrathecally or epidurally, midazolam produces analgesia which is GABA mediated. Muscle relaxation produced by midazolam is due to potentiation of glycine action on the anterior horn cells.

PHARMACODYNAMICS:

CENTRAL NERVOUS SYSTEM:

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnestic properties. It decreases the cerebral metabolic rate and cerebral blood flow. Cerebral perfusion pressure decrease as the systemic pressure falls more than the intracranial pressure. Given in doses of 0.25mg/kg it does not alter intracranial tension and therefore it can be used for neurosurgical procedures. Emergence from induction is more rapid than diazepam, but not so, when compared with thiopentone Midazolam decreases the anaesthetic requirement of inhalational agents.

CARDIOVASCULAR SYSTEM:

Midazolam decreases the myocardial contractility and systemic vascular resistance and causes vasodilatation, thus causing fall in arterial pressure. The fall in blood pressure is similar to that caused by hypnotic doses of thiopentone,greater than that caused by equipotent doses of diazepam and less than that caused by propofol. It increases the heart rate.

Midazolam does not abolish the stress response to intubalion, but the increase in heart rate and blood pressure are less than seen with diazepam. Midazolam dose not alter coronary vascular resistance and dose not cause coronary steal phenomenon.

RESPIRATORY SYSTEM:

Midazolam causes dose dependent depression of ventilation. In doses used for premedication or sedation, it dose not alter the carbondioxide response, but in doses above 0.2mg/kg it causes respiratory depression. Apnoea produced by midazolam is dose related and is more common in patients premedicated with opioids, in chronic obstructive pulmonary disorder patients, and following faster injection of the drug, Their respiratory depression is reversed by flumazenil but not by naloxone.

INTRATHECAL MIDAZOLAM:

Spinal midazolam produces analgesia by binding to specific benzodiazepine receptors in the dorsal horn of the spinal cord. Musclerelaxation is by potentiating the effect of glycine which is an inhibitory neurotransmitter to the anterior horn cells.

IN VITROCHANGES IN TRANSPARENCY AND $_{P}$H OF CSF CAUSED BY ADDING MIDAZOLAM:

CSF $_{P}$H was decreased below 7.0 by adding more than 3mg of midazolam., CSF transparency was decreased by adding more than 7mg of midazolam. Midazolam in saline neither decreased the pH nor reduced the transparency. The pharmacokinetics of intrathecal midazolam depend on the molecular weight, lipid solubility and the systemic vascular absorbtion.

ANTAGONIST OF MIDAZOLAM:

Flumazenil is an imidazo benzodiazepine, with specific benzodiazepine antagonist activity. Flumazenil binds with high affinity to specific sites when it competitively antagonizes the binding and allosteric effects of benzodiazepine. The intravenous administration of 0.3 to 1mg of

flumazenil is usually sufficient to abolish the effects of therapeutic doses of benzodiazepines within 1to2 minutes. Additional doses may be required after 1 to 2 hours.

USES OF MIDAZOLAM:

1. Premedication dose is 0.05 mg/kg to 0.1 mg/kg intramuscularly or 10-15 mg per oral. I has predictable absorption after intramuscular injection. It produces amnesia, anxiolysis and sedation.
2. Intravenous sedation dose is 0.05 mg/kg to 0.1 mg/kg. Sedation occurs

   without loss of air way reflexes, causes no vomiting and post operative

   drowsiness is less.
3. Induction dose is 0.15mg/kg to 0.3mg/kg and induction is faster than with

   diazepam.
4. **DAY CARE SURGERY:** Because of rapid onset and brief half-life midazolam is a suitable drug. But patients should not drive vehicles for at least eight hours as midazolam affects psychomotor

function and postoperative instructions should be written down.

5. Midazolam can be used in treatment of emergence phenomenon

DRUG INTERACTIONS:

Erythromycin, clarithromycin and flucanozole increase the effect of midazolam due to inhibition of cytochrome P450 III A enzyme. H_2 receptor antagonist also inhibit cytochrome P450 III A enzyme. Asprin and probenecid increase the effect by competing for protein binding site. Phenytoin, rifampicin and xanthines decrease the efficacy of midazolam due to increased metabolism by inducing cytochrome P450.

SIDE EFFECTS:

Nausea and vomiting are minimal. Incidence of hiccough is 5.6%, cough1.5%.

REVIEW OF LITERATURE

1. A comparative study of intra-thecal fentanyl and midazolam for prevention of nausea-vomiting during caesarean delivery under spinal anaesthesia was done by Dr.Pallab Rudra,Dept. of Anaesthesiology,Calcutta National Medical College and Hospital,Kolkatta. They concluded that co-administration of fentanyl 12.5 μg or midazolam 2 mg in the sub-arachnoid space avoid intra-operative discomfort during peritoneal traction and exteriorization of the uterus and thereby reduce the incidence of intra-operative and early post-delivery nausea-vomiting in caesarean section under spinal anaesthesia with 0.5% hyperbaric bupivacaine. The study is published in Indian Journal of Anaesthesia,Dec 2004,Vol.48.
2. Dahlgren ,Gunnar et al 1997, observed that spinal opioids administered along with local anaesthetics in spinal anaesthesia for caesarean section decreased the requirement of intra-operative anti-emetic medication.
3. Cooper et al reported a significant reduction in intra-operative nausea with the addition of fentanyl to spinal anaesthetic for caesarean delivery. The effects are due to the dense sensory blockade achieved by the addition of opioids to local anaesthetics in spinal anaesthesia.

4. Palmer CM et al in 1995 conducted a study where 15 μg of fentanyl was added as a sole adjuvant to hyperbaric lidocaine in spinal anaesthesia in parturients undergoing caesarean delivery and concluded that the addition of fentanyl increases the duration of effective analgesia by approximately 30min.& provides a protective effect regarding nausea & vomiting in the peri-operative period.
5. Manullang T.R, Viscome CM, Pace HL observed that intra-thecal fentanyl is superior to intra-venous ondansetron for the prevention of perioperative nausea during caesarean delivery with spinal anaesthesia. This study is published in Anaesth Analg 2000;90:1162-66.
6. Sen A,Rudra A observed that intra-thecal midazolam prevents nausea-vomiting during caesarean delivery with spinal anaesthesia. The study is published in Journal of Anaesthesia and Clinical Pharmacology 2002;18:21-25.
7. Mac Donald R.L. and Young A.B. in 1981 demonstrated GABA mediated inhibition of the spinal cord neurons in vivo and in primary dissociated cell culture.
8. In 1990 Wal dovel H.J. and co-workers conducted a study on the regional cellular and sub-cellular distribution of GABA and

benzodiazepine receptors. The highest density of GABA and benzodiazepine receptors are localized as a dense band within lamina 2 of the dorsal horn with moderately high concentration in lamina 1 and 3.

9. In 1994, Australian Society for Clinical Experimental Pharmacologists and Toxicologists conducted a study on the GABA receptors and demonstrated the presence of Non-A, Non-B GABA receptors. These were known as Novel receptors. These are the receptor sites where intra-thecally administered midazolam act.
10. In 1996, Valentine J.M and co-workers compared the postoperative analgesia provided by intrathecal bupivacaine, intrathecal bupivacaine and morphine, intrathecal bupivacaine and midazolam in patients undergoing caesarean sections.The use of patient controlled analgesia was greater with plain bupivacaine group and patients given intra-thecal morphine had pruritus. Intrathecal midazolam provided useful analgesia without side effects.
11. Clinical Journal for Pain,1996 March, states that epidural and intrathecal midazolam is more effective against somatic pain.
12. A study was conducted in Dept.of Anaesthesiology,Samsung Medical Centre, Korea by M.H.Kim and Y.M.Lee which was published in

British Journal of Anaesthesia 2001, about the potentiation of analgesic effect of intrathecal bupivacaine by intrathecal midazolam. These groups of patients were randomlt allocated and control group received 5 mg of bupivacaine and 0.2 ml of 0.9% saline, second group received 5 mg of bupivacaine and 2 mag of midazolam. They concluded that time to first analgesia was significantly greater in the midazolam group than in the placebo and significantly less in patients in second group than in the third.

13. Works of Matan in 1900 combining morphine with intrathecal cocaine appears to be one among the first attempt to enhance spinal anaesthesia with spinal opioids.

    In 1901, two independent reports, one by a Japanese anaesthesiologist and the second by a Romanian Surgeon, have been published mentioning the efficacy of opioids when used in sub-arachnoid block.

    In 1965, Gate Control theory of pain proposed by Melzack and Wall focused on the importance of dorsal horn of spinal cord in the modulation of pain.

    In 1973 Pert and Snyder identified specific opiate receptors in the substantia gelatinosa of dorsal horn of spinal cord.

    In 1976, Yaksh and Reddy suggested that intrathecal opioids act at the

presynaptic receptors in the substantia gelatinosa and block the release of neuro-transmitters. This study was undertaken in rats.

In 1984, Huand H.J. Ishimain T,Yambe studied the use of intrathecal morphine for postoperative pain relief.

14. A study of effect of intra-thecal fentanyl added to hyperbaric bupivacaine for caesarean section was conducted at Dept.of Anaesthesiology, Tokyo University School of Medicine,Tokyo. 24 patients posted for elective caesarean section were allotted to receive either 15 μg of fentanyl or 0.9% normal saline added to 2 ml of 0.5% hyperbaric bupivacaine intra-thecally in right lateral decubitus position. They concluded that addition of fentanyl to intrathecal bupivacaine in parturients undergoing caesarean section improved quality of anaesthesia without producing side effects.

15. A study was published in Indian Journal of Anaesthesia 2002 about intrathecal fentanyl added to hyperbaric bupivacaine improving analgesia during caesarean section and early postoperative period. It was conducted by Dr.Biswas, Dr. Nath & Dr.Bhattacharjee.

They randomly allotted 40 parturients coming for elective caesarean section into two groups. Group 1 received 2 ml of 0.5% bupivacaine with 0.25 ml of 0.9% saline. Group 2 received 2 ml of 0.5%

bupivacaine with 12.5μg of fentanyl. They concluded that 12.5 μg of fentanyl added to intra-thecal bupivacaine could markedly improve intra-operative anaesthesia and significantly reduce the demand for post-operative analgesia with good maternal satisfaction and fetal well being.

MATERIALS AND METHODS

The study was conducted in 100 patients posted for elective and emergency surgeries after getting approval of ethical committee of Department of Anaesthesiology, Government Rajaji Hospital and Madurai Medical College,Madurai. Informed consent was obtained after explaining the procedure.

INCLUSION CRITERIA:

-Adult patients aged 25+/-5 yrs.

-ASA physical status 1&2.

-Caesarean sections.

-Ht:155+/-5 cm Wt: 55+/-5 kgs

EXCLUSION CRITERIA:

-H/o hyperemesis gravidarum

-Contra-indication to regional anaesthesia.

-Patients with GI disorders like peptic ulcer,foetal prematurity (36 wks)

-Those who have received anti-emetics 24 hrs. before surgery.

-Those who are administered methyl-ergometrine& Prostaglandin f2α intra-operatively for uterine contraction.

Patients are grouped into three groups Group F, Group M and Group B. Group F and Group M have 40 patients each and Group B has 20 patients.

Group F

0.5% Bupivacaine 1.6 cc + 0.25 ml of fentanyl (12.5µg)

Group M

0.5% Bupivacaine 1.6 cc+ 0.25 ml of midazolam (1.25 mg)

Group B

0.5% Bupivacaine 1.6cc+ 0.25 ml of normal saline.

Total volume of solution in all the three groups is 1.85 ml.

PROCEDURE

Patients were explained about the procedure.

Base-line pulse rate, blood pressure, respiratory rate were recorded.

Intra-venous line was secured with 18 G Cannula. Pre-loading was done with 15-20 ml /kg of crystalloid solution. The following emergency drugs and equipments were kept ready.

-Boyle's anaesthetic machine with oxygen cylinder.

-Laryngoscope with varied blades

-Oro-pharyngeal airway.

-Endo-tracheal tubes.

-Suction apparatus

-Drugs like atropine, adrenaline, ephedrine,dexamethasone,deriphylline, dopamine and naloxone.

Patients were put on right lateral position. Under strict aseptic precautions sub-arachnoid block was performed using 23G Quincke Babcock's needle in L3-4 interspaces. After ensuring free flow of CSF the drug was injected as per the group assigned. After injecting the drug patients were turned supine.

RECORDING DATA:

The following were recorded

1 Time of institution of subarachnoid block

2 Maximum level of sensory block achieved (which is tested by pinprick)

3 Time of onset of surgery

4 Pulse rate, blood pressure, respiratory rate and oxygen saturation were monitored every 5 minutes for the first 15 minutes, thereafter every 20 minutes for rest of the surgery and every half an hour in the post operative period.

5 Hypotension was said to have occurred, if there was a fall in blood pressure 30% from the baseline. This was treated with 100% oxygen through face mask, intravenous fluids and ephedrine in titrated doses.

6 Respiratory depression is said to have occurred if Spo2 falls to <92% or the respiratory rate falls to <8. The condition is treated by O2supplementation via face mask.

7 Discomfort, if any experienced by the patient during surgery was recorded in the intraoperative period & degree of sedation was scored .

SEDATION SCALE

i. Patient awake anxious and agitated

ii. Patient awake oriented and tranquil

iii. Patient asleep but responds to commands only

iv. Patient asleep but responds briskly to light glabellar tap or loud auditory stimuli.

v. Patient asleep but responds sluggish to light glabellar tap or loud auditory stimuli.

vi. Patient asleep with no response to stimuli.

8 Occurrence of nausea/vomiting in the intra-operative & early post-operative period was noted. Other adverse effects like rigors, respiratory depression were noted.The statistical significance was brought by student t test.

OBSERVATION AND RESULTS

The following observations were made during the intra-operative period.

DEMOGRAPHIC DATA: All the patients are matched for age, height and weight.

Age: 25+/- 5.

Height: 155+/-5 cm

Weight: 45+/-5 cm

HIGHEST DERMATOME LEVEL ACHEIVED

The maximum level of sensory block achieved was elicited with pinprick.

The maximum level achieved in each group was:

Group B: 5% of patients had sensory block upto T4.

20% of patients had sensory block upto T5.

30% of patients had sensory block upto T6.

5% of patients had sensory block upto T10.

15% of patients had sensory block upto T7.

5% of patients had sensory block upto T9.

Group F: 22% of patients had sensory block upto T4.

58% of patients had sensory block upto T5.

20% of patients had sensory block upto T6.

Group M: 13% of patients had sensory block upto T4.

20% of patients had sensory block upto T5.

67% of patients had sensory block upto T6.

Using the Chi-square test, with a `p' value of 0.00013, the values obtained are considered statistically significant.

EMETIC EPISODES

In Group F, 80% of patients had no nausea/retching or vomiting.

10% of patients had nausea.

5% of patients had both nausea& vomiting

5% of patients had only vomiting.

In Group M, none of the patients had vomiting.

In Group B, only 15% of patients had vomiting.

Hence, nausea & vomiting does'nt appear to be significantly present in any of the

groups.

PAIN

In Group M,8% of patients had intra-operative pain.

In Group B, 50% of patients had intra-operative pain.

In Group F, no patients complained of pain.

Those 8% patients in Group M complained of pain at the end of surgery

which was controlled by administering narcotics intra-venously.

RIGORS

In Group F, 13% of patients had rigors intra-operatively

In Group M, 10% of patients had rigors intra-operatively

In Group B, none of them had rigors intra-operatively.

Values in Group F& Group M are considered statistically significant with a 'p' value of 0.0201 & 0.0393 respectively when compared with the control group.

HYPOTENSION

In Group F, 25% of patients had intra-operative hypotension.

In Group M, 8% of patients had intra-operative hypotension.

In Group B, 5% of patients had intra-operative hypotension.

None of the groups had values which are considered to be statistically significant.

RESPIRATORY DEPRESSION

In Group F, 30% of patients had respiratory depression.

In Group M, 13% of patients had respiratory depression.

Both the groups were found to have a statistically significant association with 'p' values of 0.0001 & 0.0201 in comparison with control.

SEDATION

In Group F,20% of patients had sedation score of 1.

75% of patients had sedation score of 2.

5% of patients had sedation score of 3.

In Group M,8% of patients had sedation score of 1.

92% of patients had sedation score of 2.

None of the values appear to be statistically significant.

In Group B, all the patients had a sedation score of 1.

PRURITUS

In Group F, 15% of patients had pruritus;which settled on its own.

FOETAL OUTCOME

In none of the neonates, in all the 3 groups, Apgar scores were less than 6/10 in the 1^{st} min. & 8/10 in the 5^{th} min.

DISCUSSION

Nausea and Vomiting commonly occur during caesarean delivery performed under Spinal anaesthesia, and is frequently related to intra-operative hypotension, peritoneal traction and exteriorization of the uterus. These problems may be accompanied by visceral pain, that stimulate vagal afferents, which occurs despite apparently adequate dermatomal sensory blockade. Various pharmacological agents have been used prophylactically,however, either undesirable effects or cost of the agents limited their routine use.

Intrathecal lipophilic opioid,fentanyl and benzodiazepine,midazolam have been

observed to provide improved intra and post-operative analgesia and thereby decreasediscomfort from intra-operative peritoneal manipulations which may initiate emetic episodes.(Ref: Miller's TextBook of Anaesthesiology 6th edition, Wylie&Churchill TextBook of Anaesthesiology,7th edition).

In our study, none of the three groups had statistically significant incidence of nausea& vomiting. This is in agreement with the observations of Dahlgren et al, Biswas BN, Sen A.This is also in agreement with the observations of Dr.Pallab Rudra& Dr.A.Rudra. The % of patients (20) in fentanyl group with emetic episodes was more than in the remaining two

groups.This is in contrast to the observations of Dr. Pallab Rudra & Dr.A. Rudra where nausea&vomiting was less in the fentanyl group than in the midazolam group.(↓to 25% with fentanyl whereas it is ↓to only 40% with midazolam).Among Group M & Group B, 15% in Group 'B' had vomiting whereas none of the patients in Group 'M' had intra-operative nausea/vomiting.

Hypotension was present in all the three groups , but not found to be statistically significant. It was aggressively treated with IV fluids & aliquots of IV ephedrine.

Only 15% of patients in Group 'F' had pruritus,the low incidence being due to the highly lipophilic nature of the drug and the small dose used, which limited its rostral spread.This is similar to the observations of Dr.Pallab Rudra,where only 5% of the patients developed pruritus. It subsided on its own.

None of the neonates showed reduced Apgar score . Hence it is observed that the addition of either of the adjuvants (fentanyl or midazolam to Bupivacaine) does'nt have any influence on neonatal outcome.It would have been better if umbilical cord blood analysis for pH, pCO2 and base-excess were assessed to find out any subtle insults to the newborn. However,such provisions are not available at our institution.

Dilution of a solution produce a difference in volume as well as the baricity of the solution. A very dilute solution produces differential blockade characterized by autonomic blockade, minimal sensory anaesthesia and no effect on motor function. (Ref: North American Clinics – Epidural&Spinal analgesia& anaesthesia-March 1992). This is responsible for the patchiness of blockade observed in the control group. The difference in baricity also contributes to differing dermatomal levels of blockade observed in the control group.

CONCLUSION

The incidence of nausea and vomiting is found to be considerably reduced when Fentanyl or midazolam is added to Bupivacaine for spinal anaesthesia during caesarean section.

Among the two agents, midazolam is found to be superior to fentanyl in providing intra-operative comfort during visceral handling and peritoneal traction.

Adverse effects like pruritus, rigors, hypotension were not found to be statistically significant in the study group of patients whereas respiratory depression was found to be statistically significant in both the groups when compared to control group.

COMPARISON OF INTRATHECAL FENTANYL

AND MIDAZOLAM

WITH INJ.BUPIVACAINE FOR PREVENTION OF NAUSEA AND VOMITING DURING CAESAREAN DELIVERY

PROFORMA

NAME: AGE: IP.NO: HT: WT:

INVESTIGATIONS:

BLOOD GROUP: Rh: Hb%: BLOOD SUGAR: BLOOD UREA:

SUB ARACHNOID BLOCK: SPACE:L3-L4

TIME OF BLOCK: MAXIMUM LEVEL OF BLOCK:

ONSET OF SURGERY:

INDUCTION – DELIVERY TIME: mins. SKIN INCISION – DELIVERY TIME:

UTERINE INCISION – DELIVERY: mins.

DURATION OF UTERUS EXTERIORISATION: mins.

DURATION OF SURGERY: mins.

INTRA-OPERATIVE MONITORING:

TIME	PULSE	B.P	SPO_2	OTHERS

EMETIC EPISODES: NAUSEA / VOMITING / RETCHING

RESCUE ANTI EMETIC: INJ.METACLOPROMIDE 10 Mg: YES / NO

OTHER SIDE EFFECTS: PRURITIS / SHIVERING / RESP. RATE / SPO2

SEDATION SCORE:

NEONATAL OUTCOME: APGAR SCORE: AT 1 min: AT 5 min:

REMARKS

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